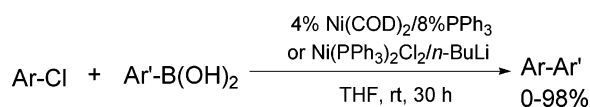# Triphenylphosphine as a Ligand for Room-Temperature Ni(0)-Catalyzed Cross-Coupling Reactions of Aryl Chlorides with Arylboronic Acids

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$$Ar\text{-}Cl \ + \ Ar'\text{-}B(OH)_2 \xrightarrow[\text{THF, rt, 30 h}]{\substack{4\% \ Ni(COD)_2/8\%PPh_3 \\ \text{or } Ni(PPh_3)_2Cl_2/n\text{-BuLi}}} \underset{0\text{-}98\%}{Ar\text{-}Ar'}$$

Room-temperature Ni(0)-catalyzed cross-coupling reactions of deactivated aryl chlorides with arylboronic acids with inexpensive triphenylphosphine (PPh₃) as a supporting ligand have been accomplished in good to excellent yields. Air-stable Ni(PPh₃)₂Cl₂ has also been established as catalyst precursor, and highly active nickel catalysts were obtained when the reduction of Ni(PPh₃)₂Cl₂ with *n*-BuLi was carried out in the presence of an aryl chloride.

Room-temperature Pd(0)-catalyzed Suzuki−Miyaura cross-coupling reactions involving deactivated aryl chlorides as coupling partners represent a remarkable advance in organometallic chemistry in recent years.[1−8] Sterically hindered, electron-rich monodentate ligands such as *t*-Bu₃P[1] and dialkylarylphosphines[2,3] and *N*-heterocyclic carbenes[4,5] have been demonstrated as a privileged group of ligands for reported catalyst systems. The bulkiness and electron-richness of these monodentate ligands are believed to be essential for the observed fast oxidative addition and reductive elimination rates. Less bulky and less electron-rich monophosphines such as PPh₃ have thus been considered as inappropriate ligands for room-temperature Suzuki−Miyaura cross-couplings of deactivated aryl chlorides. In fact, their application as efficient ligands for room-temperature Pd(0)- or Ni(0)-catalyzed Suzuki−Miyaura cross-couplings of deactivated aryl chlorides has not been established, although they have been employed as ligands for Ni(0)-catalyzed Suzuki cross-coupling reactions at elevated temperature.[1,9−11] In our laboratory, we are interested in developing highly active, cost-effective Pd(0) and Ni(0) catalysts for cross-coupling reactions involving challenging substrates including deactivated aryl chlorides and aryl/alkenyl tosylates.[7,12] On the basis of previously reported results, we know that (a) nickel is smaller and more nucleophilic than palladium, which suggests that the ligand bulkiness and electron-richness requirement for nickel might not be as stringent as that for palladium, and (b) Ni(PPh₃)₃ undergoes oxidative addition with deactivated aryl chlorides at room temperature.[13] Thus, we reasoned that less bulky and less electron-rich monophosphines such as PPh₃ might be suitable ligands for room-temperature Ni(0)-catalyzed Suzuki cross-couplings of deactivated aryl chlorides. Here, we established such a possibility.

Ni(PPh₃)₂Cl₂-catalyzed cross-couplings of deactivated aryl chlorides with arylboronic acids at elevated temperature (80−100 °C) have been previously reported.[1,10,11] Based on the fact that Ni(PPh₃)₂Cl₂- and Ni(acac)₂/PPh₃-catalyzed cross-coupling reactions of aryl chlorides with Grignard reagents, which are believed to have the same oxidative addition step as that of the Suzuki cross-coupling, occurred at room temperature,[14] we believed that the elevated temperature requirement for Ni(PPh₃)₂Cl₂-catalyzed cross-couplings of deactivated aryl chlorides with arylboronic acids might mainly serve the purposes of generating the catalytically active Ni(0) species in situ. Because the catalytically active Ni(0) species could be readily accessible from either commercially available Ni(0) complexes such as Ni(COD)₂ or reduction of Ni(II) complexes at room temperature, we reasoned that the difficulty to employ PPh₃ as an efficient room-temperature ligand might lie in how to realize the transmetalation/reductive eliminations at room temperature. Our experience in this field suggested that it would be possible

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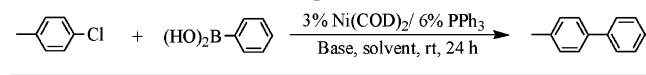(9) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.

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TABLE 1. Solvent and Base Optimization[a]

$$\text{—}\langle\bigcirc\rangle\text{—Cl} + (HO)_2B\text{—}\langle\bigcirc\rangle \xrightarrow[\text{Base, solvent, rt, 24 h}]{3\% \text{ Ni(COD)}_2/ 6\% \text{ PPh}_3} \text{—}\langle\bigcirc\rangle\langle\bigcirc\rangle$$

entry	solvent	base	conv (%)	entry	solvent	base	conv (%)
1	dioxane	K_3PO_4	27	7	THF	KF	54
2	toluene	K_3PO_4	41	8	THF	CsF	42
3	CH_2Cl_2	K_3PO_4	0	9	THF	Na_2CO_3	12
4	DMF	K_3PO_4	82	10	THF	KOH	54
5	DMA	K_3PO_4	78	11	THF	Cs_2CO_3	36
6	THF	K_3PO_4	83	12	THF	K_2CO_3	64

[a] Reaction conditions: tolyl chloride (1.0 equiv), phenylboronic acid (1.5 equiv), base (3 equiv), solvent (2 mL), room temperature.
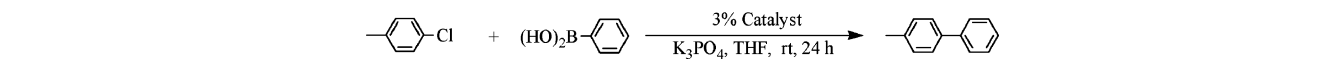
if the right combination of solvent and base was employed.[7,12] We thus screened different solvents and bases for Ni(COD)$_2$/PPh$_3$-catalyzed cross-coupling of *p*-tolyl chloride with phenylboronic acid, and the results are shown in Table 1. We found that moderate conversions were observed for dioxane and toluene, which are excellent solvents when Ni(PPh$_3$)$_2$Cl$_2$ was the catalyst at elevated temperature.[10] THF and DMF were found to be the best solvents (Table 1, entries 4 and 6). Among the bases screened, K$_3$PO$_4$ gave the best results (Table 1, entry 6). We further established that the catalyst derived from a 1:2 ratio of Ni(COD)$_2$ and PPh$_3$ gave the best results (Table 2, entries 2−5). We have also tested Ni(PPh$_3$)$_4$ as catalyst, and our results showed that its efficiency was comparable to that of Ni(COD)$_2$/PPh$_3$ system (Table 2, entry 6).

Our success in using PPh$_3$ as ligand prompted us to investigate other commercially available phosphines for this transformation, and our results are also listed in Table 2. We found that bidentate phosphines including 1,1′-bis(diphenylphosphino)ferrocene (DPPF), which has been demonstrated as an active ligand at elevated temperature for this transformation,[10b,c] were poor ligands (Table 2, entries 7 and 8). Among the monophosphines tested, only tricyclohexylphosphine showed a similar efficiency to PPh$_3$. Other monophosphines, bulkier and/or more electron-rich than PPh$_3$, only gave low to moderate conversions. These results suggested that both the size and electron-richness of the monophoshine play important roles in generating highly active room-temperature Ni(0) catalyst systems.

Under our established reaction conditions (Ni(COD)$_2$/PPh$_3$ as catalyst, THF as solvent and K$_3$PO$_4$ as base), electron-rich, as well as electron-deficient, aryl chlorides with one or none substituent at the ortho position coupled efficiently with arylboronic acids and our results are shown in Table 3. However, very sterically hindered 1-chloro-2,6-dimethylbenzene was found to be inert substrate (Table 3, entry 12). For comparison

purposes, a catalyst derived from more electron-rich PCy$_3$, i.e., Ni(COD)$_2$/PCy$_3$, has also been studied, and the data are also listed in Table 3. Our study showed that although the overall efficiency of Ni(COD)$_2$/PPh$_3$ is comparable to that of the Ni(COD)$_2$/PCy$_3$ system, our NMR study suggested that these two catalyst systems behave differently toward the oxidative addition with 4-chloroanisole. We found that Ni(COD)$_2$/4PCy$_3$ smoothly underwent oxidative addition with 4-chloroanisole to yield the oxidative addition product, which reacted with phenylboronic acid to give the coupling product in 100% conversion. This oxidative addition product was observed as the intermediate when mixing Ni(COD)$_2$, PCy$_3$, PhB(OH)$_2$, and K$_3$PO$_4$ in THF to give the coupling product, suggesting that the oxidative addition step should not be the slow step. In contrast, although Ni(PPh$_3$)$_3$ was reported to undergo oxidative addition with 4-chloroanisole at room temperature,[13] we were unable to obtain the oxidative addition product in a pure form. ^{1}H NMR showed that the oxidative addition was slow and the oxidative addition product started to decompose before the reaction completed. However, Ni(COD)$_2$/PPh$_3$ catalyst did catalyze the cross-coupling reaction of *p*-chloroanisole with phenylboronic acid (Table 3). These observations suggest that the oxidative addition step in Ni(COD)$_2$/PPh$_3$ catalyst system might be the rate-determining one.
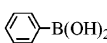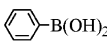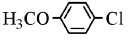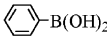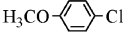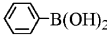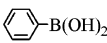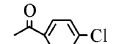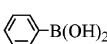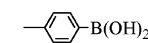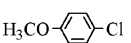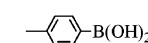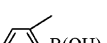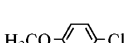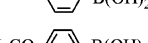
Since Ni(COD)$_2$ is more expensive and air-sensitive than Ni(PPh$_3$)$_2$Cl$_2$, we also sought to use Ni(PPh$_3$)$_2$Cl$_2$ as catalyst precursor for the reaction. We found that although Ni(PPh$_3$)$_2$Cl$_2$ and Ni(PPh$_3$)$_2$Cl$_2$/Zn[15] were ineffective catalysts, the catalyst generated from Ni(PPh$_3$)$_2$Cl$_2$/*n*-BuLi[10b,d] was as efficient as that of Ni(COD)$_2$/PPh$_3$ (Table 3, entries 2 and 4). Interestingly, we observed that the catalytic property of the nickel species generated from the reduction of Ni(PPh$_3$)$_2$-Cl$_2$ with *n*-BuLi was highly dependent on how it was produced: the reduction of Ni(PPh$_3$)$_2$Cl$_2$ with *n*-BuLi in the presence of aryl chloride generated highly active catalyst, while catalytically inactive species were obtained when the reduction of Ni(PPh$_3$)$_2$Cl$_2$ with *n*-BuLi was carried out in the absence of aryl chloride. Such phenomena suggested that the newly generated low-valent nickel species could not be stabilized by monodentated PPh$_3$ alone and could aggregate if no trapping reagent—aryl chlorides, which could undergo oxidative addition with the new generated nickel species—was present. These observations were consistent with reported results of cross-coupling reactions carried out at elevated temperature that catalysts generated from in situ reduction of Ni(DPPF)Cl$_2$ with *n*-BuLi or Grignard reagents were more efficient catalysts than that from Ni(PPh$_3$)$_2$Cl$_2$ because bidentate DPPF might stabilize the in situ generated nickel catalysts better than monodentate PPh$_3$.[10,16]

TABLE 2. Room-Temperature Nickel(0)-Catalyzed Cross-Couplings of *p*-Tolyl Chloride with Phenylboronic Acid[a]

$$\text{—}\langle\bigcirc\rangle\text{—Cl} + (HO)_2B\text{—}\langle\bigcirc\rangle \xrightarrow[\text{K}_3\text{PO}_4, \text{THF}, \text{ rt, 24 h}]{3\% \text{ Catalyst}} \text{—}\langle\bigcirc\rangle\langle\bigcirc\rangle$$

entry	catalyst	conv (%)	entry	catalyst	conv (%)
1	Ni(COD)$_2$	0	8	Ni(COD)$_2$ + 2 DPPE[b]	3
2	Ni(COD)$_2$ + PPh$_3$	44	9	Ni(COD)$_2$ + 1−4 Cy$_3$P	74−88
3	Ni(COD)$_2$ + 2 PPh$_3$	83	10	Ni(COD)$_2$ 1−4 *n*-Bu$_3$P	35−50
4	Ni(COD)$_2$ + 3 PPh$_3$	78	11	Ni(COD)$_2$ + 1−4 *i*-Bu$_3$P	24−40
5	Ni(COD)$_2$ + 4 PPh$_3$	70	12	Ni(COD)$_2$ + 1−4 *t*-Bu$_3$P	0
6	(PPh$_3$)$_4$Ni	77	13	Ni(COD)$_2$ + 1−2 *o*-Tolyl$_3$P	21−43
7	Ni(COD)$_2$ + 1−2 DPPF	9−13			

[a] Reaction conditions: aryl chlorides (1.0 equiv), phenylboronic acid (1.5 equiv), K$_3$PO$_4$(3 equiv), THF (2 mL), room temperature. [b] DPPE: 1,2-bis(diphenylphosphino)ethane.

TABLE 3. Room-Temperature Nickel(0)-Catalyzed Cross-Couplings of Aryl Chlorides with Arylboronic Acids[a]

$$\text{Ar—Cl} + (\text{HO})_2\text{B—Ar'} \xrightarrow[\text{K}_3\text{PO}_4,\ \text{THF, rt, 30 h}]{4\%\text{Ni(COD)}_2/\text{Phosphine}} \text{Ar-Ar'}$$

Entry	Ar-X	Ar'-B(OH)₂	Yield (%)[b] 8% PPh₃	16% PCy₃
1	CH₃—C₆H₄—Cl	C₆H₅—B(OH)₂	91	95
2	CH₃—C₆H₄—Cl	C₆H₅—B(OH)₂	88[c]	-
3	H₃CO—C₆H₄—Cl	C₆H₅—B(OH)₂	92	92
4	H₃CO—C₆H₄—Cl	C₆H₅—B(OH)₂	90[c]	-
5	(dimethylphenyl)—Cl	C₆H₅—B(OH)₂	80	77
6	(acetylphenyl)—Cl	C₆H₅—B(OH)₂	98	99
7	CH₃—C₆H₄—Cl	CH₃—C₆H₄—B(OH)₂	95	92
8	H₃CO—C₆H₄—Cl	CH₃—C₆H₄—B(OH)₂	93	86
9	CH₃—C₆H₄—Cl	(isopropylphenyl)—B(OH)₂	90	92
10	H₃CO—C₆H₄—Cl	(isopropylphenyl)—B(OH)₂	87	80
11	CH₃—C₆H₄—Cl	H₃CO—C₆H₄—B(OH)₂	89	-
12	(dimethylphenyl)—Cl	C₆H₅—B(OH)₂	0	

[a] Reaction conditions: aryl chlorides (1.0 equiv), arylboronic acids (1.5 equiv), Ni(COD)₂PPh₃ (4 mol %/8 mol %) or Ni(COD)₂/PHy₃ (4 mol %/16 mol %), K₃PO₄ (3 equiv), THF (2 mL), room temperature. [b] Isolated yields (average of tow runs). [c] 4 mol % of Ni(PPh₃)₂Cl₂/n-BuLi was used as catalyst.

In summary, we have demonstrated that widely available, inexpensive PPh₃ as well as PCy₃ can be used as efficient ligands for room temperature Ni(0)-catalyzed cross-coupling reactions of deactivated aryl chlorides with arylboronic acids, a process that previously required the use of expensive, bulky, electron-rich monophosphines and *N*-heterocyclic carbenes. We have also established that air-stable Ni(PPh₃)₂Cl₂ can be used as catalyst precursor and observed that the catalytic properties of the in situ generated nickel catalyst is highly dependent on how it was generated, with highly active nickel catalyst obtained when the reduction of Ni(PPh₃)₂Cl₂ with *n*-BuLi was carried out in the presence of an aryl chloride.

Experimental Section

General Procedure for the Suzuki Couplings of Aryl Chlorides with Arylboronic Acids. Method A. In a glovebox with N₂ atmosphere, to a mixture of arylboronic acid (0.75 mmol), potassium phosphate (1.5 mmol), aryl chloride (0.5 mmol), and 2 mL of THF (in a vial) were added bis(1,5-cyclooctadiene)nickel(0) (5.5 mg, 0.02 mmol) and triphenylphosphine (11 mg, 0.04 mmol). The mixture was allowed to stir for 30 h. After being quenched with water, the reaction mixture was extracted with ethyl acetate. The organic phase was washed with brine, and the solvent was evaporated under vacuum. Flash chromatography on the silica gel (hexane/acetate = 100:0 to 85:15) yielded the cross-coupling products.

Method B. In a glovebox with N₂ atmosphere, to a mixture of bis(triphenylphosphine) nickel(II) chloride (13 mg, 0.02 mmol), aryl chloride (0.5 mmol), and 2 mL of THF (in a vial) was added *n*-butyllithium (20 *µ*L, 2.5 M in hexane). After the mixture was stirred for 10 min (the solution turned deep red), phenylboronic acid (0.75 mmol) and potassium phosphate (1.5 mmol) were added. The mixture was allowed to stir for 30 h. After being quenched with water, the reaction mixture was extracted with ethyl acetate. The organic phase was washed with brine, and the solvent was evaporated under vacuum. Flash chromatography on the silica gel (hexane/acetate = 100:0 to 85:15) yielded the cross-coupling products.

Supporting Information Available: General experimental procedure for Ni(0)-catalyzed cross-coupling of aryl chlorides with arylboronic acids and characterization of the cross-coupling products and intermediate. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052369I

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